Original Article

Clinical and laboratory predictors of outcome in cerebral malaria in suburban Nigeria

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Abstract

Introduction: Cerebral malaria (CM) is an important cause of morbidity and mortality among children living in the tropics. The present study was conducted to update the knowledge on cerebral malaria in children.

Methodology: This was a prospective study conducted between June 2009 and February 2010. Consecutive children who met the clinical and parasitological diagnostic criteria for CM were admitted and studied. Demographic, essential history, clinical examination findings and laboratory results were recorded and analyzed. Outcome in survivors (presence or absence of neurological deficits) were determined at discharge.

Results: Out of 1,202 children admitted during the study period, 66 (5.5%) had CM: 40 boys and 26 girls. Ages ranged from 2 to 128 months (mean: 41.6±27.1months). Fever (100%), coma (100%) and convulsion (89%) were the commonest presenting symptoms, while unsteady gait, speech, auditory and visual impairment were the commonest neurological deficits at discharge. Fifty-seven (86.4%) patients survived while nine (13.6%) died. Of the 57 survivors, 35 (61.4%) recovered completely, while 22 (38.6%) had neurological deficits at discharge. Identified clinical and laboratory predictors of mortality in CM included: age less than 3 years ($p = 0.031$), abnormal breathing pattern ($p = 0.023$), absent corneal reflex ($p = 0.005$), absent pupillary reflex ($p = 0.047$), retinal haemorrhage ($p = 0.029$), hypoglycaemia ($p = 0.002$) and leucocytosis ($p = 0.040$).

Conclusion: CM is associated with high mortality and serious sequelae. Affected children should be given proactive management and monitored closely to reduce the frequency of adverse outcomes.

Key words: cerebral malaria; predictors; children; Nigeria

J Infect Dev Ctries 2013; 7(8):600-607. doi:10.3855/jidc.2769

(Received 28 May 2012 – Accepted 16 October 2012)

Introduction

Malaria, a common cause of morbidity and mortality among children, constitutes 25% to 40% of all outpatient clinic visits and 21% of hospital admissions in sub-Saharan Africa with over one million dying annually [1].

Cerebral malaria (CM) is the most severe neurological presentation of acute *falciparum* malaria. It is a diffuse encephalopathy associated with seizures in at least 80% of patients [2]. The case fatality rate ranges between 5% and 50% [2]. Although many survivors make a full recovery, neurological sequelae such as hemiplegia, speech problems, cortical blindness and epilepsy occur in 3% to 31% [2,3,4]. Uncontrolled seizure activity, including non-convulsive seizure, is known to damage the brain by aggravating hypoxia, hypoglycaemia and intracranial hypertension [5].

The clinical and laboratory indicators of poor prognosis in CM documented in various studies include: age younger than 3 years; deep coma; convulsions; absent corneal reflexes; body rigidity; opisthotonus; signs of cardiac, respiratory and renal function impairment; optic disc and retinal oedema; hyperparasitaemia; leucocytosis; severe anemia; hypoglycemia; low cerebrospinal fluid (CSF) glucose; elevated blood urea; creatinine; CSF and venous lactic acid; serum aspartate; aminotransferases; 5´ nucleosidases; TNF alpha level; and low anti-thrombin III [6,7].

A trend of increasing burden of CM has been documented in Ibadan, South-Western Nigeria [8]. This is particularly disturbing in view of increasing

awareness and control measures mounted against malaria locally and globally[8].Activities at controlling malaria in Nigeria have, however, been non-uniform in terms of availability of insecticide-treated nets, use and availability of artemisin combination therapy, and case management. These discrepancies may probably be responsible for poor control of malaria in varying regions of Nigeria and the evolution of the malaria parasite in the face of different standards for control and treatment of malaria. Thus malaria disease needs to be reviewed from time to time even in the same centre and sub-region [8].

Our experiences in clinical practice show that case management of both complicated and uncomplicated malaria in Ado-Ekiti is not uniform. Some patients with cerebral malaria still use chloroquine for treatment of their malaria, either from leftover home stock, pharmaceutical shops, or private hospitals. Furthermore, some children present late with cerebral malaria and other clinical conditions such as anaemia, hypoglycemia and seizures, which can affect the outcome in these patients. Thus the present study was undertaken to assess the prevalence and features of the disease and especially the clinical and laboratory correlates of its outcome.

The present study was conducted in the Children Emergency Ward (CEW) of Ekiti State University Teaching Hospital (EkSUTH), Ado-Ekiti. Ado-Ekiti is a rapidly expanding city with a population of 308,621 (2006 Census)[9].It is the capital of Ekiti state and a malaria holoendemic region of south-western Nigeria. The teaching hospital was established in 2008 and there is no known study of this subject that has been conducted in the hospital which has facilities for physiotherapy, ophthalmology, and other specialties.

Methodology

The study was performed at the children's emergency unit of the Ekiti State University Teaching Hospital (EkSUTH), Ado-Ekiti. It is a 15-bed ward, with an admission rate of 1,200 to 1,600 children per year. The hospital also provides tertiary health services for neighboring states such as Osun, Ondo and Ekiti, which have a population of at least three million people each. The age limit for admission is 15 years and the department had no intensive care unitat the time of the study. Consecutive children admitted to the CEW between 1 June 2009 and 28 February 2010, who had coma on admission or subsequent deterioration in their level of consciousness after admission and demonstrable asexual *Plasmodium falciparum* in the peripheral blood after excluding other causes of altered sensorium or coma, were diagnosed as cerebral malaria and studied [7]. Ethical clearance from the hospital and consent from the parents/caregivers were obtained.

Information was obtained with respect to the details of cerebral malaria, followed by detailed clinical examination which included anthropometry, general and systemic examinations, and fundoscopy. Nutritional status was assessed according to the modified Wellcome classification [10]. Children with weight below 60% of the expected weight for age with oedema were classified as marasmic kwashiorkor, while those with weight below 60% of the expected weight for age without oedema were classified as marasmic. Children with presence of oedema and weight between 60% and 80% of the expected weight for age were classified as kwashiorkor, while those without oedema and weights between 60% and 80%of the expected weight for age were regarded as underweight. Children with weight between above 80% of the expected weight for age without oedema were regarded as those with normal nutrition. Level of consciousness was assessed using Blantyre's coma scale for children [11].

At presentation blood was taken from each patient for full blood count, thin and thick film for malaria parasite, random blood sugar, and electrolyte/urea. Cerebrospinal fluid was also obtained for chemistry and microbiology laboratory examination. Blood film for malaria parasites was monitored daily while other investigations were repeated if the initial results were abnormal or when the patients' clinical condition dictated a need for repeat. The blood films for malaria parasite were examined and reported for specie type and parasite density and the patients were observed until discharge or death.

Patients were treated with intravenous quinine dihydrochloride. The patients were discharged from the hospital when they had improved clinically and were able to continue their treatment orally at home. Thereafter, they were followed up at the children's outpatient, ophthalmology, and physiotherapy clinics until they were considered fully recovered or were lost to follow-up.

Patients were grouped based on the presence or absence of some selected clinical and laboratory factors [*e.g.*, fever; duration and depth of coma; presence and character of convulsion; posturing; retinal hemorrhage; corneal reflex; level of parasite count; leucocytosis (total white blood cell count > 12,000/mm^3; hypoglycemia (blood sugar < 2mmol/l);

acidosis (HCO_3 < 18 mmol/l, and anemia (PCV < 30%)]. Patients with leucocytosis further had their blood samples taken for blood culture and sensitivity. They were initially started on empiric broad spectrum antibiotics in line with the expected causes of sepsis in our area and this was later reviewed and based on reports of the initial culture and sensitivity. Patients were also grouped based on the outcome (*e.g.*, complete recovery, survived with neurological deficit(s), and death).

Data was analyzed using SPSS 11.0 for Windows (SPSS Inc, Chicago, USA). Tests for association with chi square (χ^2) or predictors of outcome with logistic regression stating the 95% confidence interval were performed. Tests for trends were also conducted. The Student *t* test was used to compare means of parametric data. *P* values less than 0.05 were regarded as significant.

Results

Of the 1,202 patients (657 males and 545 females) admitted during the study period, 66 (5.5%) children had CM and 268 other children were treated for other forms of severe malaria.

General characteristics

The ages of the 66 patients ranged from 2 to 128 months with the mean age (SD) of 41.6 (27.1) months. Of the 66 patients, 49 (74.2%) were under five years old while 17 (25.8%) were five years old and above. Forty (60.6%) were males and 26 (39.4%) were females, giving a male-to-female ratio of 1.7:1. Six (9.1%) of the affected children were below one year of age. Table 1 shows the age and sex distribution of CM patients

Clinical findings

All the CM patients had been ill for periods varying from one to 14 days with a median of 3.0 days. All 66 children had a history of fever while 46 (69.7%) had one or more convulsions before presentation. Although all the children were unconscious as at the time of diagnosis of cerebral malaria, only 48 (72.7%) presented with loss of consciousness. The mean duration of loss of consciousness and fever before presentation in the hospital was 10 hours and 3 days respectively. Table 2 shows the presenting symptoms. None of the complaints was significantly associated with mortality. Table 3 also shows clinical examination findings at presentation in relation to mortality in children with CM. Abnormal breathing pattern, absent corneal reflex, absent pupillary reflex, and retinal hemorrhage were significantly associated with higher mortality (*P* < 0.05).

The weight of the children ranged from 4.5 kg to 34.0kg with a mean (SD) of 13.7 kg (5.5). Four (7.7%) of the 52 children with normal weight for age, three (27.3%) of the 11 underweight children, and the two (100%) children who were marasmic died. There was a trend for increased mortality with severity of under-nutrition (χ^2 for trend = 12.92, df = 1, p = 0.000).The axillary temperature of the 66 children at presentation ranged from 35.3° to 40.5°C with a mean (SD) of 38.1°C (1.6). Coma was common to all patients at diagnosis. Forty-five (68.2%) children were deeply comatose (Blantyre's score of 0-2) while the remaining 21 (31.8%) had light coma (Blantyre's score of 3-4) at admission. Also, 46 (69.7%) were unconscious for less than 48 hours, 14 (21.2%) for 48 to 96 hours and the remaining six (9.1%) for more than 96 hours. Among the 57 survivors, fever resolution time following treatment was within 48 hours in 44 (77.2%) children, while the remaining 13 (22.8%) had fever beyond 48 hours.

Laboratory findings

The packed cell volume of the 66 children ranged from 06% to 39% with a mean (SD) of 23.5% (8.1). All the children had the asexual form of *Plasmodium falciparum* parasitaemia with counts ranging from 50 to 300,000 parasites per µl of blood on admission and a mean (SD) of 16,058 (59,549.5). The parasite clearance time for 41 (71.9%) of the 57 survivors was within 48 hours and for the remaining 16 (28.1%), after 48 hours of commencing treatment. Their total white blood cell count (WBC) ranged from 4,300 to 40,600 cells/mm^3. The mean (SD) total WBC was 13,111 cells/ mm^3 (6,790). Twenty-three (34.8%) children had leucocytosis (WBC greater than 12,000 cells/mm^3). Table 4 shows that, of all the analyzed laboratory parameters, only hypoglycaemia and leucocytosis were significantly associated with death in CM (p < 0.05).

Outcome

Nine of the 66 children died while the remaining 57 (86.4%) survived, giving a case fatality rate of 13.6%. Of the 57 who survived, 35 (61.4%) recovered fully while 22 (38.6%) had one or more neurological deficits. Table 5 shows that ataxia, speech impairment, hearing impairment, and cortical blindness were the commonest neurological deficits recorded in the survivors of CM.

Table 1. Age and Sex Distribution of CM Patients

Age (years)	Male	Female
0-3	18	15
>3-5	12	5
>5-10	9	6
>10	1	0
Total	**40**	**26**

Table 2. Presenting complaints in relation to mortality in 66 children with CM

Presenting complaints	Number of patients	Number who died (%)	Number who survived (%)	X^2 (df=1)	P value
Fever	66	9 (13.6)	57 (86.4)	-	-
Loss of Consciousness	66	9 (13.6)	57 (86.4)	-	-
Convulsions	59	8 (13.6)	51 (86.4)	0.000	1.000
Vomiting	5	1 (20.0)	4 (80.0)	0.000	0.532
Restlessness	4	1 (33.3)	3 (66.7)	0.000	0.452
Brown urine	3	0 (0.0)	3 (100.0)	0.000	1.000

Table 3. Clinical examination findings in relation to mortality in 66 children with CM

Clinical signs	Number of patients (n=66)	Number who died (n=9)	Number who survived (n=57)	X^2 (df =1)	P value
Hyperpyrexia	16	2	14	0.000	0.676
*Abnormal breathing pattern	15	5	10	4.414	**0.023**
Tachypnoea	32	7	25	2.351	0.079
Tachycardia	47	7	40	0.005	1.000
Hepatomegaly	55	7	48	0.000	0.638
Splenomegaly	29	6	23	1.247	0.166
**Abnormal posturing	16	3	13	0.071	0.676
Absent cornea reflex	7	4	3	8.792	**0.005**
Absent pupillary reflex	3	2	1	7.595	**0.047**
Retinal haemorrhage	6	3	3	4.403	**0.029**
Papilloedema	5	0	5	0.061	1.000

*Abnormal breathing pattern includes Kussmaul and Chyne-stokes breathing
**Abnormal posturing includes decerebrate and decorticate posturing
[Fisher's exact test applied]

Table 4. Laboratory findings in relation to mortality in the 66 children with CM

Laboratory findings	Number of patients (n=66)	Number who died (n=9)	Number who survived (n=57)	P value
Severe anaemia (PCV<15%)	21	4	17	0.450
Hypoglycaemia (RBS< 2.2mmol/L)	6	4	2	**0.002**
Acidosis (HCO3< 20mmol/L)	22	5	17	0.107
High serum urea (urea>6.0mmol/L)	10	2	8	0.299
Leucocytosis (WBC>12,000cells/mm^3)	23	6	17	**0.040**
Hyperparasitaemia(>250,000/microlitre)	3	0	3	1.000

PCV = packed cell volume; RBS = random blood sugar; HCO3 = serum bicarbonate; WBC = white blood cell count

Table 5. The neurological deficits recorded among the 57 survivors

Neurological deficits	Number of patients with neurological deficits	Percentage (%) (N=57)
*Ataxia	14	24.56
Speech impairment	6	10.52
Cortical blindness	5	8.77
Hearing impairment	5	8.77
Hemiparesis	3	5.26
Spastic quadriplegia	1	1.75
Spastic triplegia	1	1.75
Quadriparesis	1	1.75
Left-sided ptosis	1	1.75

*Ataxia: a broad term describing unsteadiness in gait, disturbance in control of posture and movement and not necessarily implying cerebellar dysfunction[2,14]

Binary logistic regression analysis of some clinico-laboratory predictors of mortality in cerebral malaria

Based on the chi-square test of association, clinical and laboratory findings such as age younger than 3 years, marasmus, abnormal breathing pattern (Kussmaul and Chyne-stokes), deep coma (Blantyre's score 0-2), absent cornea reflex, absent pupillary reflex, retinal haemorrhage, hypoglycaemia, and leucocytosis had statistically significant associations with mortality (p value < 0.05). These were regressed against the outcome of death in a binary logistic regression model. Table 6 shows that all, except marasmus and deep coma, were significantly predictive of mortality in cerebral malaria.

Binary logistic regression analysis of some clinical predictors of neurological deficits (morbidity) in cerebral malaria

Coma lasting more than 48 hours was the only clinical factor found to be a significantly independent predictor of development of neurological deficits in CM (Beta coefficient = 1.306, Confidence interval = 0.027 – 0.811, p = 0.021).

Discussion

Children with CM in the present study constituted 19.8% of all the children admitted for malaria during the study period. This is similar to the figure of 19.7% reported by Orimadegun *et al*. from their study in Ibadan, South-western Nigeria, but lower than the rate of 51% documented among Gambian children by Brewster *et al*. [3,8]. The proportion of children admitted for malaria who had CM in the present study is, however, higher than the 6.3% reported by Meremikwu *et al*. in Calabar, Nigeria [12]. The higher proportion of CM patients among the Gambian children admitted for malaria can probably be explained by the fact that the Gambian study was conducted during the four-month (September to December) period of intense malaria transmission. The prevalence of CM among all children admitted for malaria in the Gambian study was also expectedly high (21%) compared to findings in other studies for

the same reason. There may be geographical differences between Nigeria and the Gambia which can also explain the differences in the transmission rates of malaria. The prevalence of cerebral malaria among children hospitalized in the present study was 5.5% and is within the range of 1% to 27% reported in other studies within and outside Nigeria [3,7,8,13].

Children aged five years and below are the most susceptible to CM. They form 75.8% of the affected children in the present study, which is in keeping with the documented range of findings in Sokoto (64.1%), Calabar (73.3%), Kenya (82.3%) and Ile-Ife (92.8%) [7,12,13,14]. However, children aged 5 year to 11years were also affected, although to a lesser extent, as previously documented [7,12,13]. This observation calls for intensified efforts to prevent malaria in the under-five years age group of children and to develop a high index of suspicion to encourage prompt treatment of CM in those older than five years in malaria holoendemic regions. The present study also shows that CM is less prevalent in children below one year of age as only six (9.1%) of the studied patients were less than one year of age, and this is within documented prevalence for this age group by other researchers [7,12,13,14]. Common reasons given to explain the low prevalence of malaria in children below one year of age include: acquired passive immunity from immune mothers through the placenta, high foetal haemoglobin which retards growth of malaria parasites, and deficiency of paraaminobenzoic acid (PABA) in breast milk which is essential for the replication of *P. falciparum* [7].

The presenting clinical features of fever, convulsion and loss of consciousness in the patients were similar to features documented in other studies [7,12,13]. The mean duration of fever and unconsciousness before presentation was three days and 10 hours, respectively, indicate a rapid progression of uncomplicated malaria to cerebral malaria, and this observation is consistent with the findings reported by Jiya *et al*, and Molyneux *et al*, [2,7]. There is, therefore, the need for health workers to be both observant and prompt in the management of uncomplicated malaria to prevent progression to CM. The other documented presenting clinical features of CM in the present study, such as vomiting, restlessness, generalized body weakness, *etc*., are similar to the findings in other studies [7,13,14]. All the children had a history of fever, as also noted earlier by Sowunmi and Elusiyan *et al*. [13,14]. The findings of normal temperatures in 28.8% of our patients at presentation imply that a normal, and even subnormal, temperature as previously stated does not exclude the possibility of CM in a child presenting with acute coma in a malaria endemic environment [6]. To aid prompt diagnosis and treatment, functional blood film laboratory facilities should be provided in all in all such centres.

Our case fatality rate of 13.6%, although within the range of 5% to 50% reported from within and outside Nigeria in previous studies, is very high and it shows that severe malaria contributes significantly to childhood mortality [2,7,13]. The difference in mortality rate in the different studies could be explained by the different study methodologies and durations; for example, the study from Ile-Ife with the lowest mortality rate was retrospective and it covered a longer duration of five years, while the other studies were prospective, covering one-year periods each. All the deaths in the present study occurred within 48 hours of admission with two-thirds occurring within 24 hours; this finding is also consistent with those documented by other African researchers and stresses the need for closer monitoring and prompt management of CM patients, especially in the first two days of presentation [2,7,14].

Although only 13 (19.7%) of the children studied were malnourished, a significantly higher proportion (38.5%) of malnourished children died compared to well-nourished children (7.5%) and the study also showed a trend of increasing mortality with severity of malnutrition. These findings are in keeping with existing knowledge that although malnourished children are less susceptible to malarial infection, when they have CM they are more likely to die than normally nourished children [15]. Olumese *et al*. reported similar findings in Ibadan, where 50% of the malnourished children had poor outcome compared to 14.2% among the well-nourished children [15]. Malnutrition is the leading cause of death in developing countries where it is directly or indirectly responsible for 54% of deaths among children under five years of age [16].Suggested reasons for a higher death rate among malnourished children die include: coexisting bacterial infections, hypoglycaemia, hypocalcaemia, hypothermia, congestive cardiac failure and overwhelming sepsis [15]. Such conditions should be carefully sought and treated when present in malnourished children with CM. However, the investigations needed to diagnose the complications of malnutrition are cost intensive and since parental poverty is a common underlying factor in protein energy malnutrition, lack of funds hampers the management of malnourished CM patients.

Malnourished children with features of severe malaria should be given malaria prophylaxis during nutritional rehabilitation in addition to other well-established therapeutic measures in their management [15]. Two of the malnourished children with CM who died had marasmus. Muller *et al*. had documented that, although there was no association between PEM and malaria morbidity, malnourished children had more than a two-fold higher risk of dying than well-nourished children [17]. Therefore, the combination of PEM and CM in a child must be viewed as a harbinger of death to the child, meaning that both must be managed promptly, efficiently and aggressively.

The spectrum of neurological deficits observed in the 57 survivors is similar to that documented by Molyneux *et al.* [2]. Neuronal damage could result from tissue hypoxia due to sequestered parasitized RBCs occluding micro-vessels supplying various parts of the brain, thereby giving rise to focal lesions resembling cerebro-vascular accident [3]. The most common neurological deficit at discharge was unsteadiness of gait and a disturbance in control of posture and movement not necessarily implying cerebellar dysfunction [4]. It usually resolved completely within one week of discharge from the hospital [6]. There were no observed cases of monoparesis, psychosis and attention deficit hyperactivity disorders which were reported by other investigators [12,14]. In view of the aforementioned various neurological deficits among survivors of CM, every survivor of CM should undergo thorough CNS examinations before discharge, including review and management by other specialists such as ophthalmologists, oto-rhino-laryngologists, physiotherapists, and psychologists as indicated.

Clinical and laboratory factors with statistically significant association with mortality were similar, but not identical to the predictors of mortality and development of neurological deficits in the present study. The findings in the present study of age less than three years, abnormal breathing pattern, absent corneal and pupillary reflexes, retinal haemorrhages, *etc*. as clinical and laboratory features predictive of poor outcome are consistent with the findings in other studies [2,6,7].Other clinical features in the study which were associated with but not independently predictive of mortality or development of neurological deficits in CM are marasmus and deep coma (Blantyre's score 0-2). Leucocytosis (total white blood cell count > 12,000/ mm^3), found to be an indicator of poor prognosis in this study, was also so reported by Molyneux *et al*. even in the absence of detectable secondary bacterial infection [2]. Pragmatically we gave antibiotics to children who had leucocytosis and features suggestive of septicaemia as has been suggested; however, the blood cultures taken in seven of our patients yielded no growth [6].

Some of the limitations of the present study include the inability to exhaustively study all factors that may serve as predictors in the outcome of the disease. The impact of socioeconomic factors, for instance, was not studied. It is expected that the social standing and the economic status of the family of the child will influence the ability of such a family to promptly and appropriately utilize health facilities. The influence of concomitant diseases was also not investigated in the present study and this is expected to impact negatively on the outcome.

Conclusion

In view of the high mortality and frequency of neurological sequelae associated with CM in children younger than five years of age, it is suggested that under-five CM patients in general, and especially those with any of the aforementioned clinical and laboratory predictors of poor outcome, should be targeted for proactive management and monitored closely to avoid adverse outcomes.

Acknowledgement

We appreciate all members of staff of the children's department of Ekiti State University Teaching Hospital for their contribution to the success of this study.

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Conflict of interests: No conflict of interests is declared.